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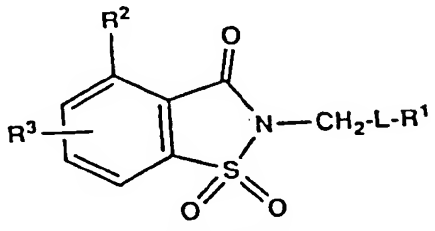
(54) **Saccharin derivative proteolytic enzyme inhibitors.**

(57) Compounds having the structural formula



Formula I

wherein
L is N,O or $SO_n$ wherein n is 0,1or 2;
$L-R^1$ is a leaving group, $H-L-R^1$ is the conjugate acid thereof and,
when L is N, $H-L-R^1$ has a $pK_a$ value less than or equal to 6,
when L is O, $H-L-R^1$ has a $pK_a$ value less than or equal to 8, and

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when L is $SO_n$, H – L – $R^1$ has a $pK_a$ value less than or equal to 5;
$R_2$ is primary or secondary alkyl of two to four carbon atoms, primary alkylamino of one to three carbon atoms, primary alkylm thylamino of two to four carbon atoms, diethylamino or primary alkoxy of one to three carbon atoms; and $R_3$ is from one to three of a variety of sustituents at any or all of the 5 –, 6 – and 7 – positions;
or a pharmaceutically acceptable acid addition salt thereof if the compound has a basic functional group or a pharmaceutically acceptable base addition salt thereof if the compound has an acidic functional group,
which inhibit the enzymatic activity of proteolytic enzymes, and processes for preparation thereof, method of use thereof in treatment of degenerative diseases and pharmaceutical compositions thereof are disclosed.

The invention relates to saccharin derivatives which inhibit the enzymatic activity of proteolytic enzymes, to processes for preparation thereof, to method of use thereof in the treatment of degenerative diseases and to pharmaceutical compositions thereof.

Inhibitors of proteolytic enzymes are useful in treatment of degenerative disorders such as emphysema, rheumatoid arthritis and pancreatitis in which proteolysis is a substantive element. Serine proteases are the most widely distributed class of proteolytic enzymes. Some serine proteases are characterized as chymotrypsin-like or elastase-like based upon their substrate specificity. Chymotrypsin and chymotrypsin-like enzymes normally cleave a peptide bond in a protein at a site at which the amino acid residue on the carbonyl side is Trp, Tyr, Phe, Met, Leu or other amino acid which contains an aromatic or a large alkyl side chain. Elastase and elastase-like enzymes normally cleave a peptide bond at a site at which the amino acid residue on the carbonyl side of the bond is Ala, Val, Ser, Leu or other small amino acid. Both chymotrypsin-like and elastase-like enzymes are found in leukocytes, mast cells and pancreatic juice in higher organisms, and are secreted by many types of bacteria, yeast and parasites.

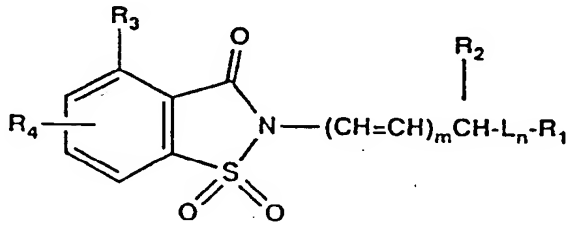
Mulvey et al. U.S. Patent 4,195,023 describes methods of inhibiting elastase and treating emphysema with 4,5,6- or 7-$R_1$-2-$R_2CO$-1,2-benzisothiazolinone-1,1-dioxide (4,5,6- or 7-$R_1$-2-$R_2CO$-saccharin) wherein $R_1$ is halogen, alkoxy, alkylamino, dialkylamino, alkoxycarbonyl, amino, nitro or especially hydrogen and $R_2$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, halophenyl, heteroaryl or substituted heteroaryl, for example 2-(2-furoyl)saccharin, and pharmaceutical compositions thereof.

Chen U.S. Patent 4,263,393 describes 2-aroylmethylsaccharins substituted or unsubstituted on aroyl and on the saccharin nucleus including for example as compound 12,2-[(p-fluorobenzoyl)methyl]-saccharin as being useful in photographic elements, film units and processes to provide electrons to immobile compounds which must accept at least one electron before releasing a diffusible dye or photgraphic reagent.

Jones et al. U.S. Patent 4,276,298 describes 2-R-1,2-benzisothiazolinone-1,1-dioxides (2-R-saccharin) wherein R is phenyl or pyridyl substituted by from one to five of fluoro, nitro except mononitro when R is phenyl, trifluoromethyl, cyano, alkoxycarbonyl, alkylcarbonyl, carboxyl, carbamoyl, alkylacylamino, alkylsulfonyl, N,N-dialkylsulfamyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfonyl and trifluoromethylsulfinyl useful in methods of inhibiting proteases, especially elastase, and of treating emphysema, rheumatoid arthritis, and other inflammatory diseases.

Reczek et al. U.S. Patent 4,350,752 describes 2-(heterocyclylmethyl)saccharins substituted or unsubstituted on heterocyclyl and on the saccharin nucleus including for example as compound 28,2-[(1-phenyltetrazol-5-yl)thiomethyl]saccharin as blocked photographic reagents.useful in photographic elements, film units and processes.

Dunlap et al. PCT Application WO 90/13549 describes saccharin derivatives useful as proteolytic enzyme inhibitors having the structural formula:




wherein:

L is -O-, -S-, -SO- or $-SO_2-$;

m and n are each independently 0 or 1;

$R_1$ is halogen, lower-alkanoyl, 1-oxo-phenalenyl, phenyl (or phenyl substituted by halogen, lower-alkyl, lower-alkoxy, nitro, amino, lower-alkylamino or di-lower-alkylamino) or heterocyclyl selected from 1H-(5-tetrazolyl), 5-oxo-1-tetrazolyl, 5-thioxo-1-tetrazolyl (when $R_2$ as defined hereinbelow is other than phenylthio), pyrimidinyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-phthalimidyl, 2-(1,3,4-thiadiazolyl), 5-(1,2,4-thiadiazolyl), 5-thioxo-3-(1,2,4-thiadiazolyl), 4-(5-oxo-1,3,4-thiadiazolyl), 4-5-thioxo-1,3,4-thiadiazolyl), 3-(1,2,4-triazolyl), 4-(1,2,4-triazolyl), (1,2,3-triazol), 2-imidazolyl or 3-(1,2,4-triazolo[4,3-a]pyridinyl), or such heterocyclyl groups substituted on any available nitrogen atom by lower-alkyl, hydroxy-lower-alkyl, cyclo-alkyl, 2-,3- or 4-pyridinyl, carboxy-lower-alkyl, lower-alkoxycarbonyl-lower alkyl, aminocarbonyl-lower-alkyl, lower-alkylaminocarbonyl-lower-alkyl, di-

lower – alkylamino – carbonyl – lower – alkyl, amino – lower – alkyl, lower – alkylamino – lower – alkyl, di – lower – alkylamino – lower – alkyl, 4 – morpholinyl – lower – alkyl, 1 – piperidinyl – lower – alkyl, 1 – pyrrolidinyl – lower – alkyl or phenyl (or phenyl substituted by amino, lower – alkylamino, di – lower – alkylamino, lower alkanamido, N – lower – alkyl – lower – alkanamido, carboxy – lower – alkanamido, carboxy, carbo – lower – alkoxy, lower alkoxy or halogen), or such heterocyclyl groups substituted on any available carbon atom by nitro, lower – alkyl, amino, lower – alkylamino, di – lower – alkylamino, cycloalkylamino, mercapto, lower – alkylthio, amino – lower – alkylthio, lower – alkylamin – lower – alkylthio, di – lower – alkylamino – lower – alkylthio, 4 – morpholinyl – lower – alkylthio, 1 – piperidinyl – lower – alkylthio, 1 – pyrrolidinyl – lower – alkythio, carbo – lower – alkoxy or phenyl (or phenyl substituted by amino, lower – alkylamino, di – lower – alkylamino, lower – alkanamido, N – lower – alkyl – lower – alkanamido, lower – alkyl, lower – alkoxy or halogen);

$R_2$ is hydrogen, carbo – lower – alkoxy, phenyl or phenylthio;

$R_3$ is hydrogen, halogen, primary or secondary lower – alkyl, lower – alkoxy, carbo – lower – alkoxy, phenyl, fluoro – lower – alkyl, lower – alkenyl or cyano;

$R_4$ is hydrogen or from one to two substituents selected from halogen, cyano, nitro, amino, lower – alkanamido, phenyl – lower – alkanamido, diphenyl – lower – alkanamido, lower – alkylsulfonylamino, polyfluoro – lower – alkylsulfonamino, aminosulfonyl, lower – alkyl, polyhalo – lower – alkyl, cycloalkyl, polyhalo – lower – alkoxy, hydroxy, lower – alkoxy, carboxy, hydroxymethyl, formyl, aminomethyl, lower – alkyl – sulfonyl, polyhalo – lower – alkyl – sulfonyl, lower – alkylsulfonylamino – sulfonyl and lower – alkoxy – poly – lower – alkyleneoxy; and wherein the $-CHR_2-$ group is always appended either to a hetero atom of the L moiety as defined above or it is appended to a hetero atom of the $R_1$ moiety, with the provisos that

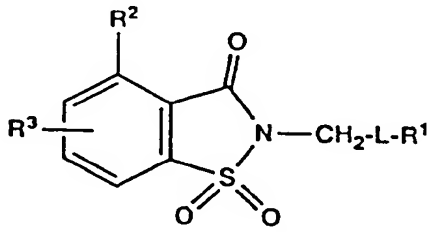
(i) when m and n are 0 and $R_2$, $R_3$ and $R_4$ are all hydrogen, $R_1$ cannot be halogen;

(ii) when m is 0, n is 1, L is –S– and $R_2$, $R_3$ and $R_4$ are each hydrogen, $R_1$ cannot be 1 – phenyl – 1H – (5 – tetrazolyl);

(iii) when m is 0, n is 1, L is –O– or –S– and $R_2$, $R_3$ and $R_4$ are all hydrogen, $R_1$ cannot be lower – alkanoyl;

(iv) when m is 0, n is 1, L is –O–, –S– or –SO–, and $R_2$, $R_3$ and $R_4$ are all hydrogen, or when m is O, n is 1, L is –S–, $R_2$ and $R_4$ are hydrogen and $R_3$ is halogen, or when m is O, n is 1, L is –SO– or $-SO_2-$, $R_2$ is carbo – lower – alkoxy and $R_3$ and $R_4$ are both hydrogen, $R_1$ cannot be phenyl or substituted phenyl.

According to one aspect of the present invention there is provided a compound having the structural formula




Formula I

wherein

L is N, O or $SO_n$ wherein n is 0, 1 or 2;

$L-R^1$ is a leaving group, $H-L-R^1$ is the conjugate acid thereof and,

when L is N, $H-L-R^1$ has a $pK_a$ value less than or equal to 6,

when L is O, $H-L-R^1$ has a $pK_a$ value less than or equal to 8, and

when L is $SO_n$, $H-L-R^1$ has a $pK_a$ value less than or equal to 5;

$R^2$ is primary or secondary alkyl of two to four carbon atoms, primary alkylamino of one to three carbon atoms, primary alkylmethylamino of two to four carbon atoms, diethylamino or primary alkoxy of one to three carbon atoms; and

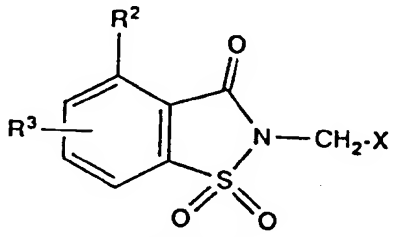
$R^3$ is from one to three substituents at any or all of the 5 –, 6 – and 7 – positions and is selected from the group consisting of hydrogen, lower – alkyl, cycloalkyl, amino – lower – alkyl, lower – alkylamino – lower – alkyl, di – lower – alkylamino – lower – alkyl, hydroxy – lower – alkyl, lower – alkoxy – lower – alkyl, perfluoro – lower – alkyl, perchloro – lower – alkyl, formyl, cyano, carboxy, aminocarbonyl, R – oxy – carbonyl, B = N wherein B = N is amino, lower – alkylamino, di – lower – alkylamino, carboxy – lower – alkylamino, 1 – pyr –

rolidinyl, 1 – piperidinyl, 1 – azetidinyl, 4 – morpholinyl, 1 – piperazinyl, 4 – lower – alkyl – 1 – piperazinyl, 4 – benzyl – 1 – piperazinyl or 1 – imidazolyl, 1 – lower – alkyl – 2 – pyrrolyl, lower – alkylsulfonylamino, perfluoro – lower – alkylsulfonylamino, perchloro – lower – alkylsulfonylamino, nitro, hydroxy, lower – alkoxy, cycloalkoxy, B = N – lower – alkoxy, hydroxy – lower – alkoxy, polyhydroxy – lower – alkoxy or acetal or ketal thereof, lower – alkoxy – lower – alkoxy, poly – lower – alkoxy – lower – alkoxy, hydroxy – poly – lower – alkyleneoxy, lower – alkoxy – poly – lower – alkyleneoxy, B = N – carbonyloxy, carboxy – lower – alkoxy, R – oxycarbonyl – lower – alkoxy, methylenedioxy, di – lower – alkylphosphonyloxy, R – thio, R – sulfinyl, R – sulfonyl, perfluoro – lower – alkylsulfonyl, perchloro – lower – alkylsulfonyl, aminosulfonyl, lower – alkylaminosulfonyl, di – lower – alkylaminosulfonyl and halo wherein R is lower – alkyl, phenyl, benzyl or naphthyl or phenyl or naphthyl having one or two substituents selected from the group consisting of lower – alkyl, lower – alkoxy and halo;

or a pharmaceutically acceptable acid addition salt thereof if the compound has a basic functional group or a pharmaceutically acceptable base addition salt thereof if the compound has an acidic functional group.

The compounds of Formula I inhibit the enzymatic activity of proteolytic enzymes and are useful in the treatment of degenerative diseases.

In another aspect of the invention there is provided a process for preparing a compound of Formula I which comprises condensing the corresponding compound having the structural formula

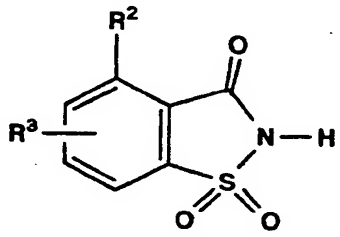


Formula II

wherein X is chloro or bromo,

with the corresponding compound of formula $H-L'-R^1$ in the presence of a base or with a corresponding basic salt of the compound of formula $H-L'-R^1$ wherein L' is N, O or S to prepare the corresponding compound of Formula I wherein L is N, O or S and then oxidizing with one molar equivalent of a peroxide or peracid the corresponding compound of Formula I wherein L is S to prepare the compound of Formula I wherein L is SO or with one or two molar equivalents of a peroxide or peracid the corresponding compound of Formula I wherein L is SO or S respectively to prepare the compound of Formula I wherein L is $SO_2$.

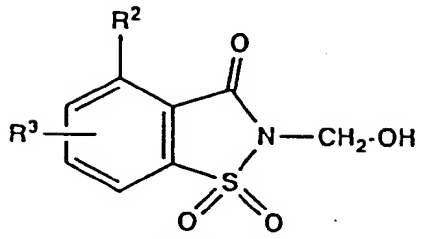
In a further aspect the invention provides a process for preparing a compound of Formula I which comprises condensing the corresponding compound of formula $X-CH_2-L'-R$, wherein X is chloro or bromo and L' is N, O or S, with the corresponding compound having the structural formula



Formula III

in the presence of a base or with a basic salt thereof to prepare the corresponding compound of Formula I wherein L is N, O or S and then oxidizing with one molar equivalent of a peroxide or peracid the corresponding compound of Formula I wherein L is S to prepare the compound of Formula I wherein L is SO or with one or two molar equivalents of a peroxide or peracid the corresponding compound of Formula I wherein L is SO or S respectively to prepare the compound of Formula I wherein L is $SO_2$.

In another aspect the invention provides a process for preparing a compound of Formula I wherein L is O and $R^1$ is acyl which comprises condensing the corresponding compound having the structural formula



Formula IV

with the corresponding acid chloride of formula Cl – $R^1$ or the corresponding acid anhydride of formula O – $(R^1)_2$ in the presence of a strong acid catalyst.

In a further aspect of the invention there is provided a process for preparing a compound of Formula I wherein L – $R^1$ is substituted or unsubstituted 1,2,3 – triazol – 1 – yl which comprises condensing the corresponding compound of Formula II with an alkali metal azide and then effecting cycloaddition of the resulting 2 – azidomethyl – 4 – $R^2$ – 5, 6 or 7 – $R^3$ – saccharin with the corresponding substituted or unsubstituted acetylene.

In yet a further aspect the invention provides the use of a compound of Formula I for preparation of a medicament for treatment of a degenerative disease in a patient in need of such treatment.

In a final aspect of the invention there is provided a pharmaceutical composition for treatment of degenerative disease which comprises a proteolytic enzyme inhibiting concentration of a compound of Formula I in a pharmaceutical carrier.

Saccharin is 1,2 – benzisothiazol – (2H) – 3 – one – 1,1 – dioxide and the compounds of Formula I, which are 2 – ($R^1$ – L – $CH_2$) – 4 – $R^2$ – (5, 6 and/or 7) – $R^3$ – 1,2 – benzisothiazol – (2H) – 3 – one – 1,1 – dioxides, are accordingly 2 – ($R^1$ – L – $CH_2$) – 4 – $R^2$ – (5, 6 and/or 7) – $R^3$ – saccharins.

In the compounds of Formulas I – IV "corresponding" means that a defined variable in one formula has the same definition in another formula.

When L is N, N taken together with $R^1$ is N – heterocyclyl, that is, N is part of a heterocyclic ring and is the atom whereby the heterocyclic ring is bonded to $CH_2$. N – Heterocyclyl is preferably monocyclic or bicyclic, substituted or unsubstituted, aromatic or hydroaromatic N – heterocyclyl, most preferably monocyclic, substituted, aromatic N – heterocyclyl, for example 4,5 – di(t – butyl – sulfonyl) – 1,2,3 – triazol – 1 – yl.

When L is O, the bond between L and $R^1$ is an ester or ester – like bond or an ether or ether – like bond. If it is an ester or ester – like bond, $R^1$ is preferably acyl, wherein acyl is lower – alkanoyl, or an amino acid or peptide acyl or cycloalkanecarbonyl; monocyclic, bicyclic or tricyclic aryl – lower – alkanoyl unsubstituted or substituted in alkanoyl by hydroxy or lower – alkoxy; monocyclic or bicyclic, substituted or unsubstituted, aromatic or hydroaromatic C – heterocyclylcarbonyl; monocyclic substituted or unsubstituted aryloxy – 2 – lower – alkanoyl or more preferably monocyclic, bicyclic or tricyclic, substituted or unsubstituted aroyl, most preferably monocyclic substituted or unsubstituted aroyl; or B' = N – carbonyl wherein B' = N is amino, lower – alkylamino, di – lower – alkylamino, aryl – lower – alkylamino, diarylamino, 1 – pyrrolidinyl, 1 – piperidinyl, 1 – morpholinyl, 1 – piperazinyl, 4 – lower – alkyl – 1 – piperazinyl or 1 – azepinyl. If it is an ester or ester – like bond, $R^1$ is also preferably (mono or di – lower – alkyl, phenyl or lower – alkoxyphenyl) – phosphinyl or (mono or di – lower – alkyl, phenyl or phenyl – lower – alkyl)phosphono. If it is an ether or ether – like bond, $R^1$ is preferably monocyclic or bicyclic, substituted or unsubstituted, aromatic or hydroaromatic C – heterocyclyl or the residue of an oxime, or more preferably monocyclic, bicyclic or tricyclic, substituted aryl; monocyclic or bicyclic, substituted or unsubstituted, aromatic or hydroaromatic 3 – oxocarbocycl – 1 – enyl or 3 – oxo – C – heterocycl – 1 – enyl.

When L is S, the bond between L and $R^1$ is a thioester or thioether or thiocarbonate bond and H – L – $R_1$ is a thioacid or thiol or thiocarbonate and $R^1$ is preferably cyano or lower – alkoxythiocarbonyl; monocyclic, bicyclic or tricyclic, substituted or unsubstituted aroyl or aryl or preferably monocyclic or bicyclic, substituted or unsubstituted, aromatic or hydroaromatic C – heterocyclyl, most preferably monocyclic, substituted, aromatic C – heterocyclyl, for example 1 – phenyltetrazol – 5 – yl.

As used herein the terms C – heterocyclyl and C – heterocyclylcarbonyl mean that the heterocyclic ring is bonded to $CH_2$ and carbonyl respectively at a carbon atom of the heterocyclic ring.

In the terms that follow the carbon chain part thereof has from one to ten carbon atoms, preferably from one to four carbon atoms, and is branched or unbranched; – lower – alkyl, perfluoro – lower – alkyl, perchloro – lower – alkyl, lower – alkoxycarbonyl, lower – alkylamino, di – lower – alkylamino, lower – alkoxy, the lower – alkylamino part of lower – alkylamino – lower – alkyl, the lower – alkylamino part of di – lower –

alkylamino – lower – alkyl, the lower – alkoxy part of lower – alkoxy – lower – alkyl, carboxy – lower – alkylamino, 4 – lower – alkyl – 1 – piperazinyl, 1 – lower – alkyl – 2 – pyrrolyl, lower – alkylsulfonylamino, perfluoro – low r – alkylsulfonylamino, perchloro – lower – alkylsulfonylamino and carboxy – lower – alkoxy, the first lower – alkoxy part of lower – alkoxy – lower – alkoxy, the first lower – alkoxy part of poly – lower – alkoxy – lower – alkoxy, the lower – alkoxy part of lower – alkoxy – poly – lower – alkyleneoxy, R – oxycarbonyl – lower – alkoxy, perfluoro – lower – alkylsulfonyl, perchloro – lower – alkylsulfonyl, lower – alkylaminosulfonyl and di – lower – alkylaminosulfonyl

However in the following terms the carbon chain part thereof has from two to ten carbon atoms, preferably from two to four carbon atoms, and is branched or unbranched; – amino – lower – alkyl, the lower – alkyl part of lower – alkylamino – lower – alkyl, the lower – alkyl part of di – lower – alkylamino – lower – alkyl, hydroxy – lower – alkyl, the lower – alkyl part of lower – alkoxy – lower – alkyl, the lower – alkoxy part of B = N – lower – alkoxy, hydroxy – lower – alkoxy, polyhydroxy – lower – alkoxy,the second lower – alkoxy part of lower – alkoxy – lower – alkoxy, the second lower – alkoxy part of poly – lower – alkoxy – lower – alkoxy, the alkyleneoxy part of hydroxy – poly – lower – alkyleneoxy, the alkyleneoxy part of lower – alkoxy – poly – lower – alkyleneoxy and lower – alkanoyl.

Alkylene is preferably 1,2 – alkylene. Cycloalkyl, cycloalkoxy and cycloalkanecarbonyl have from three to six ring carbon atoms and can be

Alkylene is preferably 1,2 – alkylene. Cycloalkyl, cycloalkoxy and cycloalkanecarbonyl have from three to six ring carbon atoms and can be substituted by one or more lower – alkyl. Halo is fluoro, chloro, bromo or iodo. Monocyclic aryl is phenyl, bicyclic aryl is naphthyl and tricyclic aryl is anthracyl or phenanthryl. Monocyclic aroyl is benzoyl, bicyclic aroyl is naphthoyl and tricyclic aroyl is anthracenoyl or phenanthrenoyl. Aryl and aroyl can be substituted by lower – alkyl, lower – alkoxy or halo. 3 – Oxocarbocycl – 1 – enyl and 3 – oxo – C – heterocycl – 1 – enyl have from four to ten ring carbon atoms and can be substituted by one or more lower – alkyl or other substituent.

$R^2$ is preferably primary or secondary alkyl of two to four carbon atoms.

$R^3$ is preferably hydroxy, lower – alkoxy, cycloalkoxy, B = N – lower – alkoxy, hydroxy – lower – alkoxy, polyhydroxy – lower – alkoxy or acetal or ketal thereof, lower – alkoxy – lower – alkoxy, poly – lower – alkoxy – lower – alkoxy, lower – alkoxy – poly – lower – alkyleneoxy, B = N – carbonyloxy, carboxy – lower – alkoxy, R – oxy – carbonyl – lower – alkoxy, methylenedioxy or di – lower – alkylphosphonyloxy and, except methylenedioxy, is preferably located at the 6 – position. Methylenedioxy can be located at the 5 and 6 – or 6 and 7 – positions.

In carrying out the preparation of a compound of Formula I from a corresponding compound of Formula II and the corresponding compound $H – L' – R^1$ or a corresponding compound of Formula III and the corresponding compound $X – CH_2 – L' – R^1$ in the presence of a base, the base can be any base which is not itself a reactant under the reaction conditions and is preferably an alkali metal carbonate, an alkali metal alkoxide, a tri – lower – alkylamine, a thallous lower – alkoxide, 1,8 – diazabicyclo – [5.4.0]undec – 7 – ene or 7 – methyl – 1,5,7 – triazabicyclo – [4.4.0]dec – 5 – ene. Under the reaction conditions the base may form the basic salt of $H – L' – R^1$ or the compound of Formula III, which then reacts with the compound of Formula I or $X – CH_2 – L' – R^1$ respectively. The basic salt of $H – L' – R^1$ or the compound of Formula III can also be formed separately and then condensed with the compound of Formula II or $X – CH_2 – L' – R^1$ respectively and is preferably an alkali metal, especially cesium, or thallous salt thereof. The condensation is carried out in an organic solvent or mixture of organic solvents inert under the reaction conditions, for example acetone, methyl ethyl ketone, acetonitrile, tetrahydrofuran, diethyl ether, dimethylformamide, N – methylpyrrolidone, dichloromethane, xylene, toluene or a lower – alkanol or mixture thereof, at a

In carrying out the preparation of a compound of Formula I from a corresponding compound of Formula IV and the corresponding acid chloride $Cl – R^1$ or the corresponding acid anhydride $O(R^1)_2$, the strong acid catalyst is any strong acid catalyst which does not otherwise react with the compound of Formula I or the compound of Formula IV, for example sulfuric acid or p – toluenesulfonic acid. The condensation is carried with or without an organic solvent inert under the reaction conditions or a mixture thereof at a temperature of 0 – 100 °C.

A compound of Formula 1 wherein L is SO or $SO_2$ can be prepared using any peroxide or peracid which does not oxidize any other part of the molecule in an inert solvent with or without heating or cooling. The preferred peroxide or peracid is m – chloroperbenzoic acid.

In preparing a compound of Formula I wherein $L – R^1$ is substituted or unsubstituted 1,2,3 – triazol – 1 – yl the alkali metal azide is preferably sodium azide. Condensation of the corresponding compound of Formula II with the alkali metal azide is carried out with or without heating or cooling, preferably at room temperature, in an inert solvent, for example benzene, toluene or dimethylformamide, optionally using a crown ether, for example 18 – crown – 6 ether. Cyclization of the resulting 2 – azidomethyl – 4 – $R^2$ – 5, 6 or

7 – $R^3$ – saccharin with the corresponding substituted or unsubstituted acetylene is preferably carried out in the same inert solvent with heating.

The compounds of Formulas II, III and IV and of formulae H – L – $R^1$, X – $CH_2$ – L – $R^1$, Cl – $R^1$ and O – $(R^1)_2$ are known or are made by known methods or by methods described below.

A compound of Formula III can be prepared by diazotizing the corresponding lower – alkyl 2 – amino – 3, 4 or 5 – $R^3$ – 6 – $R^4$ – benzoate ester, chlorosulfonylating the resulting lower – alkyl 3, 4 or 5 – $R^3$ – 6 – $R^4$ – benzoate ester 2 – diazonium salt with sulfur dioxide and cuprous chloride, and cyclizing the resulting lower – alkyl 2 – chlorosulfonyl – 3, 4 or 5 – $R^3$ – 6 – $R^4$ – benzoate ester with ammonia. Hydroxymethylation of the resulting compound of Formula III with formaldehyde affords the corresponding compound of Formula IV, displacement of whose hydroxyl with chloride or bromide using, for example thionyl chloride, thionyl bromide, phosphorus trichloride or phosphorus tribromide affords the corresponding compound of Formula II.

A compound of Formula II can also be prepared by phenylthiomethylating the corresponding compound of Formula III or basic salt thereof with phenyl chloromethyl sulfide and displacing phenylthio from the resulting 2 – phenylthiomethyl – 4 – $R^2$ – 5, 6 or 7 – $R^3$ – saccharin with chloride or bromide using, for example, sulfuryl chloride or sulfuryl bromide.

A compound of Formula II wherein X is chloro can also be prepared in one step from the corresponding compound of Formula III by chloromethylation with paraformaldehyde and chlorotrimethylsilane in the presence of stannic chloride.

A compound of Formula III can also be prepared by lithiating the corresponding 2 – $R^2$ – 3, 4 or 5 – $R^3$ – N,N – di – lower – alkylbenzamide with a lower – alkyl lithium, aminosulfonylating the resulting 2 – $R^2$ – 3, 4 or 5 – $R^3$ – 6 – lithio – N,N – di – lower – alkylbenzamide with sulfur dioxide followed by hydroxylamine O – sulfonic acid or sulfuryl chloride and then ammonia, and cyclizing the resulting 2 – $R^2$ – 3, 4 or 5 – $R^3$ – 6 – aminosulfonyl – N,N – di – lower – alkylbenzamide in refluxing acetic acid.

A compound of Formula III wherein $R^2$ is primary or secondary alkyl of two to four carbon atoms can be prepared by lithiating the corresponding 4 – methyl – 5, 6 or 7 – $R^3$ – saccharin with two molar equivalents of a lower – alkyl lithium in an inert solvent, for example tetrahydrofuran (THF) and alkylating the resulting 4 – lithiomethyl – 5, 6 or 7 – $R^3$ – saccharin with the appropriate alkyl halide. Both reactions are carried out at a temperature in the range from – 80 °C. to – 50 °C. The above – described 2 – $R^2$ – 3, 4 or 5 – $R^3$ – N,N – di – lower – alkylbenzamide wherein $R^2$ is primary or secondary alkyl of two to four carbon atoms can be prepared by a similar lithiation – alkylation sequence starting with the corresponding 2 – methyl, ethyl or propyl – 3, 4 or 5 – $R^3$ – N,N – di – lower – alkylbenzamide.

A compound of Formula III wherein $R^2$ is primary or secondary. alkyl of two to four carbon atoms can also be prepared by introducing $R^2$ earlier in the synthesis. Conjugate addition of the appropriate $R^2$ – cuprate to 2 – cyclohexenone and methoxycarbonylation of the resulting copper enolate with methyl cyanoformate gives the corresponding 2 – methoxycarbonyl – 3 – $R^2$ – cyclohexanone. Enol etherification with benzylthiol and acidic clay gives a mixture of the corresponding 6 – $R^2$ – 2 – benzylthio – 1 – cyclohexenecarboxylic acid methyl ester and 6 – $R^2$ – 2 – benzylthio – 3 – cyclohexenecarboxylic acid methyl ester, aromatization of which with dichlorodicyanobenzoquinone gives the corresponding 2 – $R^2$ – 6 – benzylthiobenzoic acid methyl ester. Oxidation – chlorination – debenzylation of this with chlorine in aqueous acetic acid gives 2 – $R^2$ – 6 – chlorosulfonylbenzoic acid methyl ester, cyclization of which with ammonia gives the corresponding 4 – $R^2$ – saccharin of Formula III.

Preparation of certain compounds of Formula III requires building up both rings thereof. For example, to prepare a compound of Formula III wherein $R^2$ is lower – alkoxy and $R^3$ is hydroxy, 3,3 – thiobispropionic acid is converted with thionyl chloride into the bis acid chloride. This is converted with benzylamine into the bis benzylamide, which on cyclization with sulfuryl chloride gives 5 – chlor – 2 – benzyl – 2H – isothiazol – 3 – one. Oxidation with one molar equivalent of a peracid gives 5 – chloro – 2 – benzyl – 2H – isothiazol – 3 – one – 1 – oxide, which on heating under pressure with a 2 – lower – alkoxyfuran gives a 4 – lower – alkoxy – 7 – hydroxy – 2 – benzyl – 1,2 – benzoisothiazol – 2H – 3 – one – 1 – oxide. Oxidation with one molar equivalent of a peracid gives the corresponding 4 – lower – alkoxy – 7 – hydroxy – 2 – benzyl – 1,2 – benzoisothiazol – 2H – 3 – one – 1,1 – dioxide, which on debenzylation by catalytic hydrogenation gives the corresponding 4 – lower – alkoxy – 7 – hydroxysaccharin of Formula III. Alkylation of a thus prepared 4 – lower – alkoxy – 7 – hydroxy – 2 – benzyl – 1,2 – benzoisothiazol – 2H – 3 – one – 1 – oxide with a lower – alkyl halide or an appropriately substituted lower – alkyl halide followed by oxidation and debenzylation similarly affords the corresponding 4 – lower – alkoxy – 7 – $R^3$ – saccharin of Formula III wherein $R^3$ is lower – alkoxy, cycloalkoxy, B = N – lower – alkoxy, hydroxy – lower – alkoxy, polyhydroxy – lower – alkoxy or acetal or ketal thereof, lower – alkoxy – lower – alkoxy, poly – lower – alkoxy – lower – alkoxy, hydroxy – poly – lower – alkyleneoxy or lower – alkoxy – poly – lower – alkyleneoxy.

In preparing a compound of Formula I wherein L – $R^1$ is substituted or unsubstituted 1,2,3 – triazol – 1 – yl from the corresponding 2 – azidomethyl – 4 – $R^2$ – 5, 6 or 7 – $R^3$ – saccharin, condensation of the corresponding compound of Formula II with the alkali metal azide, preferably sodium azide, is carried out in an inert solvent, for example benzene or toluene, at a temperature of 0 – 150 °C. Without isolation the resulting 2 – azidomethyl – 4 – $R^2$ – 5, 6 or 7 – $R^3$ – saccharin is cyclized with the corresponding substituted or unsubstituted acetylene in the same solvent at a temperature of 0 – 150 °C. to give the compound of Formula I.

The pharmaceutically acceptable acid or base addition salt can be any pharmaceutically acceptable acid or base addition salt but preferably has a common anion, for example the hydrochloride salt, or common cation, for example the sodium or potassium salt, respectively. If the salt having a common anion or cation is unacceptable because it is not crystalline or insufficiently soluble or hygroscopic, a salt having a less common anion, for example the methanesulfonate, or less common cation, for example the diethylammonium salt, can be used. In any event for use in a mammal the acid or base addition salt must be nontoxic and must not interfere with the elastase inhibitory effect of the free base or acid form respectively of the compound of Formula I.

The $pK_a$ values of the compounds of formula H – L – $R^1$ are known or can be determined by any of several known methods, for example as described by Adrien Albert and E.P. Serjeant (The Determination of Ionization Constants, A Laboratory Manual, Third Edition, Chapman and Hall, London and New York, 1984) by titration in water (chapters 2 and 3) or by ultraviolet spectrophotometric determination in water (chapter 4), or can be estimated from known or thus determined $pK_a$ values of closely related compounds. CRC Handbook of Chemistry and Physics (72nd Edition, CRC Press, Inc., Boca Raton – Ann Arbor – Boston, 1991, pp. 8 – 39 and 8 – 40) presents dissociation constants and pK ($pK_a$ values of several hundred organic acids. G. Kortüm, W. Vogel and K. Andrussow (Dissociation Constants of Organic Acids in Aqueous Solutions, Butterworths, London, 1961) presents dissociation constants of 1,056 organic acids.

In the preparations and examples described below structures of products are inferred from known structures of starting materials and expected courses of preparative reactions. Purification or purity and structural confirmation of starting materials and products were carried out or measured by melting temperature range (m.r.), optical rotation, elemental analysis, infrared spectral analysis, ultraviolet spectral analysis, mass spectral analysis, nuclear magnetic resonance spectral analysis, gas chromatography, column chromatography, high pressure liquid chromatography, medium pressure liquid chromatography and/or thin layer chromatography (t.l.c).

The following examples illustrate the present invention but in no way are to be seen as limiting the scope thereof.

Example 1

Preparation of Starting Material 2 – Chloromethyl – 4 – isopropyl – 6 – methoxysaccharin [II; $R^2$ = i – Pr, $R^3$ = 6 – MeO, X = Cl]

(a) 2 – Aminosulfonyl 6 – isopropyl – 4 – methoxy – N,N – diethylbenzamide

To a solution of 300 mL N,N,N',N' – tetramethylethylenediamine (1.99 moles) in 4 L anhydrous ether was added 1550 mL sec – BuLi (1.3 M) and the mixture was cooled to – 70 °C under a nitrogen atmosphere. A solution of 454.2 g 2 – isopropyl – 4 – methoxy – N,N – diethylbenzamide (1.82 moles) in 300 mL anhydrous ether was added dropwise over 30 minutes The temperature was maintained at or below – 60 °C during the addition. After the addition the mixture was stirred at – 70 °C for one hour, allowed to warm to – 50 °C, held at – 50 °C for 30 minutes, then cooled back to – 70 °C. By cannulation tube a solution of 200 g $SO_2$ in 200 mL dry ether precooled to – 40 °C was added under positive nitrogen pressure over a 20 – minute period. The temperature of the reaction mixture during the addition was maintained below – 40 °C. A white powdery precipitate of aryllithium sulphinate separated out almost immediately.

After the addition the cooling bath was removed and the mixture was stirred at ambient temperature for two hours, then cooled to – 5 °C. With continued stirring 190 mL sulfuryl chloride (2.36 moles) was added dropwise over a 15 – minute period while maintaining the temperature below 10 °C. After further stirring for 30 minutes at 0 – 5 °C., a white insoluble precipitate was filtered off and washed with 2 L anhydrous ether. Removal of the solvent at atmospheric pressure afforded the resulting sulfonyl chloride (a crude dark oil) which was dissolved in 1.4 L THF. The solution was cooled to – 10 °C., and 540 mL concentrated aqueous ammonia (28%) was added in portions over 15 minutes. The temperature was kept at 15 °C. or below throughout the addition. After stirring for 15 minutes at ambient temperature the THF and excess ammonia

were removed under vacuum to give a dark oil, which was diluted with 6.0 L water and acidified with 3N HCl to pH 1. The resulting light yellow solid was collected by filtration, washed with 800 mL of water, dried at 60 ° C. und r vacuum for 18 hours and recrystallized from a mixture of 800 mL ethyl acetat and 3 L hexane to give 429.6g (72%) of 2 – aminosulfonyl – 6 – isopropyl – 4 – methoxy – N,N – diethylbenzamide, m.r. 122 – 125 ° C.

(b) 4 – Isopropyl 6 – methoxysaccharin

A solution of 429.6 g of the diethylbenzamide (1.31 mole) in 1.5 L acetic acid was refluxed for 20 hours, then cooled to room temperature. The solvent was removed under vacuum. The oily residue was dissolved in 6 L water and the pH was adjusted to 1 with 6N HCl. The crude product was collected by filtration, washed with 2 L water, dried at 60 ° C. under vacuum for 18 hours and recrystallized from ethyl acetate/hexane to give 303 g (91%) 4 – isopropyl – 6 – methoxysaccharin, m.p. 188 ° C.

(c) 2 – Chloromethyl – 4 – isopropyl – 6 – methoxysaccharin

To a suspension of 24 g paraformaldehyde (0.8 mole) and 86.4 g chlorotrimethylsilane (1.6 moles) in 200 mL 1,2 – dichloroethane was added 0.8 ml anhydrous tin(IV) chloride and the resulting solution stirred on a steam bath for one hour. 4 – Isopropyl – 6 – methoxysaccharin (51.4 g, 0.2 mole) was added to the clear solution and the mixture was refluxed for 18 hours, cooled to room temperature and poured into water. The organic layer was separated, washed with 50 mL 2N sodium hydroxide solution, dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was purified by crystallization from ethyl acetate/hexane to give 57 g (87%) of 2 – chloromethyl – 4 – isopropyl – 6 – methoxysaccharin, m.p. 151 ° C.

Preparation of Compounds of Formulae I 2 – [4,5 – Di(t – butylsulfonyl) – 1,2,3 – triazol – 1 – yl]methyl – 4 – isopropyl – 6 – methoxysaccharin

[I; $R^2$ = iPr, $R^3$ = 6 – MeO, L – $R^1$ = 4,5 – di(t – $BuSO_2$) – 1,2,3 – triazol – 1 – yl)]

A solution of 18 – crown – 6 ether (0.60 g) and benzene (60 mL) was heated under reflux with a water separator for 1 hour, then cooled to room temperature. 2 – Chloromethyl – 4 – isopropyl – 6 – methoxysac – charin (3.03 g) and sodium azide (0.65 g) were added, and the mixture was stirred for a week at room temperature, then chromatographed on a column of silica gel (silica gel 60, 83 g) using benzene as eluant. The fractions containing the product, which were identified by t.l.c, were combined and concentrated affording 2 – azidomethyl – 4 – isopropyl – 6 – methoxysaccharin as a solution in benzene (250 mL).

Di(t – butylsulfonyl)acetylene (1.50 g) was added to part (75 mL) of the solution of 2 – azidomethyl – 4 – isopropyl – 6 – methoxysaccharin in benzene. The resulting solution was heated under reflux for 65 hours, then chromatographed on silica gel (Kieselgel 60, 68 g) using first benzene and then cyclohexane – ethyl acetate (90:10, then 85:15, then 75:25) as eluant. The fractions containing the product, which were identified by t.l.c, were combined and recrystallized from benzene – cyclohexane. Part (0.5 g) of the resulting product (1.5 g, m.r. 204 – 205 ° C., 26% yield for both steps) was recrystallized twice from ethyl acetate affording 2 – [4,5 – di(t – butylsulfonyl) – 1,2,3 – triazol – 1 – yl]methyl – 4 – isopropyl – 6 – methoxysaccharin as pale yellow elongated prisms (0.15 g, m.r. 207.5 – 209 ° C.).

By titration in water the $pK_a$ values of 1,2,3 – triazole – 4,5 – dinitrile and 1,2,3 – triazole – 4,5 – dicarbox – ylic acid dimethyl ester were determined to be 1.6 and 4.4 respectively. By ultraviolet spectrophotometric determination in water the $pK_a$ value of 1,2,3 – triazole – 4,5 – dicarboxamide was determined to be 5.3. By comparison with these $pK_a$ values the $pK_a$ value of 4,5 – di(t – butylsulfonyl) – 1,2,3 – triazole is estimated to be about 2 or less.

Example 2

2 – {2,6 – Dichloro – 3 – [2 – (4 – morpholinylethoxy)]benzoyloxymethyl} – 4 – isopropyl – 6 – methoxysaccharin

[I; $R^2$ = iPr; $R^3$ = 6 – MeO, L = O, $R^1$ – 2,6 – di – Cl – 3 – [2 – (4 – morpholinylethoxy) – benzoyl]

A mixture of 2 – chloromethyl – 4 – isopropyl – 6 – methoxysaccharin (3.12 g), 2,6 – dichloro – 3 – [2 – (4 – morpholinylethoxy)]benzoic acid (3.0 g), potassium carbonate (1.93 g) and tetrabutylammonium bromide (0.75 g) in dimethylformamide (50 mL) was heated at 75 ° C. for 1.5 hours, cooled to room temp rature, and

poured into water (400 ml.). The resulting precipitate was collected by filtration, washed with water (200 mL) and hexane (200 mL), and dried affording 2-{2,6-dichloro-3-[2-(4-morpholinylethoxy)]-benzoyloxymethyl}-4-isopropyl-6-methoxysaccharin (6.1 g; theory, 5.50 g).

Similar condensation of 2-chloromethyl-4-isopropyl-6-methoxysaccharin and 2,6-dichlor-3-[2-(4-morpholinylethoxy)]benzoic acid with potassium carbonate in N-methylpyrrolidone at room temperature and recrystallization of the product from ethanol afforded 2-{2,6-dichloro-3-[2-(4-morpholinylethoxy)]benzoyloxymethyl}-4-isopropyl-6-methoxysaccharin in 69% yield (m.p. 146°C.).

Saturated ethereal hydrogen chloride was added to a solution of 2-{2,6-dichlor-3-[2-(4-morpholinylethoxy)]benzoyloxymethyl}-4-isopropyl-6-methoxysaccharin (4.6 g from the first above-described preparation thereof) in ether-dichloromethane (9:1, 100 mL). The resulting precipitate was collected by filtration, washed with ether and cyclohexane, and dried affording 2-{2,6-dichloro-3-[2-(4-morpholinylethoxy)]benzoyloxymethyl}-4-isopropyl-6-methoxysaccharin hydrochloride salt (3.9 g, 89% yield for both steps).

By comparison with known $pK_a$ values of known substituted benzoic acids the $pK_a$ value of 2,6-dichloro-3-[2-(4-morpholinylethoxy)]benzoic acid is estimated to be from about 2 to about 3.

Example 3

2-(1-Phenyltetrazol-5-yl)thiomethyl-4-isopropyl-6-methoxysaccharin

[I; $R^2$ = iPr, $R^3$ = 6-MeO, L = S, $R^1$ = 1-phenyltetrazol-5-yl]

A mixture of 2-chloromethyl-4-isopropyl-6-methoxysaccharin (0.25 g) and 1-phenyltetrazole-5-thiol sodium salt (0.173 g) in dimethylformamide (10 mL) was heated at 60°C-80°C. for 8 hours, then poured into ice-water containing saturated aqueous sodium bicarbonate. The resulting mixture was extracted with ether. The ether extract was washed with water and saturated aqueous sodium chloride, passed through silica gel and stripped of ether affording 2-(1-phenyltetrazol-5-yl)thiomethyl-4-isopropyl-6-methoxysaccharin as a foam (0.3 g, 83% yield).

By ultraviolet spectrophotometric determination in water the $pK_a$ value of 1-phenyltetrazole-5-thiol was determined to be 2.9.

Example 4

2-(1-Phenyltetrazol-5-yl)sulfinylmethyl-4-isopropyl-6-methoxysaccharin

[I; $R^2$ = iPr, $R^3$ = 6-MeO, L = SO, $R^1$ = 1-phenyltetrazol-5-yl]

Oxidation of 2-(1-phenyltetrazol-5-yl)thiomethyl-4-isopropyl-6-methoxysaccharin with one molar equivalent of m-perbenzoic acid in an inert solvent gives 2-(1-phenyltetrazol-5-yl)-sulfinylmethyl-4-isopropyl-6-methoxysaccharin.

Example 5

2-(1-Phenyltetrazol-5-yl)sulfonylmethyl-4-isopropyl-6-methoxysaccharin

[I; $R^2$ = iPr, $R^3$ = 6-MeO, L = $SO_2$, $R^1$ = 1-phenyltetrazol-5-yl]

Oxidation of 2-(1-phenyltetrazol-5-yl)sulfinylmethyl-4-isopropyl-6-methoxysaccharin with one molar equivalent of m-perbenzoic acid in an inert solvent gives 2-(1-phenyltetrazol-5-yl)-sulfonylmethyl-4-isopropyl-6-methoxysaccharin.

Example 6

2 – (4 – Phenyl – 5 – thiono – 4,5 – dihydrotetrazol – 1 – yl)methyl – 4 – isopropyl – 6 – methoxysaccharin

[I; $R^2$ = iPr, $R^3$ = 6 – MeO, L – $R^1$ = – N – N = N – N(Ph) – C(= S) –, wherein the first N is bonded to C]

Condensation of 4 – isopropyl – 6 – methoxysaccharin sodium salt with 2 – chloromethyl – 4 – phenyl – 5 – thiono – 4,5 – dihydrotetrazole in dimethylformamide with heating gives 2 – (4 – phenyl – 5 – thiono – 4,5 – dihydrotetrazol – 1 – yl)methyl – 4 – isopropyl – 6 – methoxysaccharin.

Example 7

2 – Acetoxymethyl – 4 – isopropyl – 6 – methoxysaccharin

[I; $R^2$ = iPr, $R^3$ = 6 – MeO, L = O, $R^1$ = $CH_3CO$]

Condensation of 4 – isopropyl – 6 – methoxysaccharin with aqueous formaldehyde in ethanol gives 2 – hydroxymethyl – 4 – isopropyl – 6 – methoxysaccharin, acetylation of which with acetic anhydride and a catalytic amount of sulfuric acid gives 2 – acetoxymethyl – 4 – isopropyl – 6 – methoxysaccharin.

Additional examples of the compounds of Formula I have been prepared by the methods described above and in above – cited applications Serial No. 07/514,920 and Serial No. 07/782,016 and are described below in terms of the variables $R^2$, $R^3$ and L – $R^1$.

Compounds of Formula I have been prepared wherein $R^2$ is ethyl, n – propyl, isopropyl, 2 – butyl, dimethylamino, methoxy, ethoxy, and isopropoxy.

Compounds of Formula I have been prepared wherein $R^3$ is hydrogen, 7 – methyl, 6 – (4 – methyl – 1 – piperazinyl), 6 – (1 – methyl – 2 – pyrrolyl), 6 – dimethylamino, 5 – nitro, 6 – nitro, 6 – hydroxy, 7 – hydroxy, 5 – methoxy, 6 – methoxy, 7 – methoxy, 5,6 – dimethoxy, 5,7 – dimethoxy, 6,7 – dimethoxy, 6 – ethoxy, 6 – isopropoxy, 6 – cyclobutyloxy, 6 – [2 – (4 – morpholinyl)ethoxy] 6 – [(2,3 – dihydroxy) – propoxy], 6 – [(2,3 – propylenedioxy)propoxy], 6 – [2,3 – dimethoxypropoxy], 6 – [2 – (2 – methoxyethoxy)ethoxy], 7 – [2 – (2 – methoxyethoxy)ethoxy], 7 – carboxymethoxy, 6 – methoxycarbonylmethoxy, 6 – (t – butoxycarbonyl)methoxy, 6 – benzyloxycarbonylmethoxy, 7 – (t – butoxycarbonyl)methoxy, 7 – dimethylaminocarbonyloxy, 6,7 – methylenedioxy, 6 – fluoro, 7 – chloro, 6 – (n – propyl) – 7 – methoxy, 6 – methyl – 5,7 – dimethoxy, 5 – hydroxy – 6 – methoxy and 6 – dimethylamino – 7 – chloro.

Compounds of Formula I wherein L is N and N taken together with $R^1$ is N – heterocyclyl have been prepared wherein N – heterocyclyl is 4,5 – di(t – butylsulfonyl) – 1,2,3 – triazol – 1 – yl, 4 – phenyl – 5 – thiono – 4,5 – dihydrotetrazolyl – 1 – yl, 4 – (3 – pyridyl) – 5 – thiono – 4,5 – dihydrotetrazolyl – 1 – yl, 1,1,3 – trioxotetrahydro – 1,2,5 – thiadiazol – 2 – yl, 4,5 – di(methoxycarbonyl) – 1,2,3 – triazol – 1 – yl, 4 – phenylsulfonyl – 1,2,3 – triazol – 1 – yl, 4 – methoxycarbonyl – 1,2,3 – triazol – 1 – yl, 5 – methoxycarbonyl – 1,2,3 – triazol – 1 – yl, 4 – phenyl – 5 – ethoxycarbonyl – 1,2,3 – triazol – 1 – yl, 4 – ethoxycarbonyl – 5 – phenyl – 1,2,3 – triazol – 1 – yl, 4 – carboxy – 1,2,3 – triazol – 1 – yl, 4 – trimethylsilyl – 5 – phenylsulfonyl – 1,2,3 – triazol – 1 – yl, 5 – phenylsulfonyl – 1,2,3 – triazol – 1 – yl, 4 – phenylsulfonyl – 5 – isopropyl – 1,2,3 – triazin – 1 – yl, 4 – isopropyl – 5 – phenylsulfonyl – 1,2,3 – triazol – 1 – yl 4,5 – di(aminocarbonyl) – 1,2,3 – triazol – 1 – yl, 4,5 – dicarboxy – 1,2,3 – triazol – 1 – yl, 4,5 – dicarboxy – 1,2,3 – triazol – 1 – yl (monosodium salt), 4 – trimethylsilyl – 5 – dimethylaminosulfonyl – 1,2,3 – triazol – 1 – yl, 2 – thiono – 2,3 – dihydro – 5 – (2 – pyridyl) – 1,3,4 – thiadiazol – 3 – yl, 4 – (t – butyl) – 5 – dimethylaminosulfonyl – 1,2,3 – triazol – 1 – yl, 4 – dimethylaminosulfonyl – 5 – (t – butyl) – 1,2,3 – triazol – 1 – yl, 4 – trimethylsilyl – 1,2,3 – triazol – 1 – yl, 4,5 – dicyano – 1,2,3 – triazol – 1 – yl, 4,5 – di(1 – piperidinylcarbonyl) – 1,2,3 – triazol – 1 – yl, 4,5 – di – (trifluoromethyl) – 1,2,3 – triazol – 1 – yl, 4,5 – di(1 – piperidinylcarbonyl) – 1,2,3 – triazol – 2 – yl, 3 – benzyloxy – 4,5 – dihydro – 5 – oxo – 1,2,4 – oxadiazol – 4 – yl and 4,5 – dicyano – 1,2,3 – triazol – 2 – yl.

A compound of Formula I wherein L is O and $R^1$ is lower – alkanoyl has been prepared wherein lower – alkanoyl is 2,2 – dimethylpropanoyl.

A compound of Formula I wherein L is O and $R^1$ is an amino acid or peptide acyl has been prepared wherein peptide acyl is (N – benzoylglycyl) – phenylalanyl.

A compound of Formula I wherein L is O and $R^1$ is cycloalkanecarbonyl has been prepared wherein cycloalkanecarbonyl is cyclopropanecarbonyl.

Compounds of Formula I wherein L is O and $R^1$ is aryl – lower – alkanoyl unsubstituted or substituted by hydroxy or lower alkoxy have been prepared wherein substituted or unsubstituted aryl – lower – alkanoyl is 2 – methyl – 2 – phenylpropanoyl, 2 – methyl – 2 – (4 – chlorophenyl)propanoyl, 2 – (2 – chlorophenyl) – pro –

panoyl, 2 – hydroxy – 2 – phenylacetyl, 2 – methoxy – 2 – phenylacetyl or 2 – hydroxy – 2 – phenylpropanoyl.

Compounds of Formula I wherein L is O and $R^1$ is monocyclic, substituted or unsubstituted, aromatic or hydroaromatic C – heterocyclylcarbonyl have been prepared wherein C – heterocyclylcarbonyl is 3,5 – dichloropyridyl – 4 – carbonyl, 3,5 – dichloro – 2 – [2 – (4 – morpholinyl)ethoxy]pyridyl – 4 – carbonyl, 3,5 – dichloro – 2 – [2 – (dimethylamino)ethoxy]pyridyl – 4 – carbonyl, thiophene – 3 – carbonyl, 3 – methylthiophene – 2 – carbonyl, thiophene – 2 – carbonyl, 3 – chlorothiophene – 2 – carbonyl, 2 – oxopyrrolidinyl – 5 – carbonyl, 3,5 – dimethylisoxazol – 4 – carbonyl, 2,4 – dimethylpyridyl – 3 – carbonyl and 1 – phenyl – 3,5 – dimethylpyrazole – 4 – carbonyl.

A compound of Formula I wherein L is O and $R^1$ is monocyclic substituted aryloxy – 2 – lower – alkanoyl has been prepared wherein aryloxy – 2 – lower – alkanoyl is 2 – methyl – 2 – (4 – chlorophenoxy)propionyl.

A compound of Formula I wherein L is O and $R^1$ is bicyclic or tricyclic unsubstituted aroyl has been prepared wherein aroyl is 2 – naphthoyl or 4 – anthracenoyl.

Compounds of Formula I wherein L is O and $R^1$ is monocyclic substituted or unsubstituted aroyl have been prepared wherein monocyclic, substituted or unsubstituted aroyl is 2,6 – dichloro – 3 – [2 – (4 – morpholinyl) – ethoxy]benzoyl, benzoyl, 2,6 – dichlorobenzoyl, 2,6 – dichloro – 3 – (4 – morpholinylsulfonyl) – benzoyl 2,6 – dichlor – 3 – (4 – methyl – 1 – piperazinylsulfonyl)benzoyl, 2,6 – dichloro – 3 – (carboxymethylaminosulfonyl)benzoyl, 2,6 – dichloro – 3 – [N – (4 – isopropyl – 2 – saccharinylmethyl) – N – (benzyloxycarbonyl)aminosulfonyl]benzoyl, 2,6 – dichloro – 3 – (1 – piperazinylsulfonyl)benzoyl, 2,6 – dichloro – 3 – [N – (2 – dimethylaminoethyl) – N – (methyl)aminosulfonyl]benzoyl, 2,6 – dichloro – 3 – hydroxybenzoyl, 2,6 – dichlor – 3 – benzyloxybenzoyl, 3 – benzyloxybenzoyl, 2,6 – dichloro – 3 – (4 – benzyl – 1 – piperazinylsulfonyl)benzoyl, 2,6 – dichloro – 3 – carboxymethoxybenzoyl, 2,6 – dichloro – 3 – methoxybenzoyl, 2,6 – dichloro – 4 – methoxybenzoyl, 2,6 – dichloro – 3 – [2 – (dimethylamino)ethoxy]benzoyl, 2,6 – dichloro – 3 – [N – (3 – dimethylaminopropyl) – N – (methyl)aminosulfonyl]benzoyl 2,6 – di – fluoro – 3 – (4 – methyl – 1 – piperazinylsulfonyl)benzoyl, 2,4,6 – trichlorobenzoyl, 2,6 – difluorobenzoyl, 2,6 – dimethylbenzoyl, 2,4 – dichlorobenzoyl, 2,6 – dichloro – 4 – [2 – (4 – morpholinyl) – ethoxy]benzoyl, 2,6 – dichloro – 3 – [2 – (1 – pyrrolidinyl)ethoxy]benzoyl, 2,6 – dichloro – 3 – [2 – (1 – piperidinyl)ethoxy]benzoyl, 2,6 – dichloro – 3[2 – (diethylamino)ethoxy] – benzoyl, 2,6 – difluoro – 4 – methoxybenzoyl, 2,6 – dimethoxy – 4 – benzyloxybenzoyl, 2,4,6 – trimethoxybenzoyl, 2,6 – dichloro – 4 – ethoxycarbonylbenzoyl, 2 – isopropylbenzoyl, 2,6 – dimethoxy – 4 – acetylaminobenzoyl, 2,6 – dimethyl – 4 – benzyloxybenzoyl, 2,6 – dimethyl – 4 – nitrobenzoyl, 2 – isopropyl – 4 – methoxybenzoyl, 2,6 – dimethoxy – 3 – methylsulfonylaminobenzoyl and 2 – isopropyl – 4,5 – dimethoxybenzoyl.

A compound of Formula I wherein L is O and $R^1$ is aryl – lower – alkylaminocarbonyl has been prepared wherein aryl – lower – alkylaminocarbonyl is phenylmethylaminocarbonyl.

A compound of Formula I wherein L is O and $R^1$ is (mono or di – lower – alkyl, phenyl or lower – alkoxyphenyl)phosphinyl has been prepared wherein (mono or di – lower – alkyl, phenyl or lower – alkoxyphenyl)phosphinyl is diphenylphosphinyl.

A compound of Formula I wherein L is O and $R^1$ is (mono or di – lower – alkyl, phenyl or phenyl – lower – alkyl)phosphono has been prepared wherein (mono or di – lower – alkyl, phenyl or phenyl – lower – alkyl)phosphono is diethylphosphono.

Compounds of Formula I wherein L is O and $R^1$ is C – heterocyclyl have been prepared wherein C – heterocyclyl is 2 – methyl – 4 – pyron – 3 – yl, 6 – hydroxymethyl – 4 – pyron – 3 – yl, 3,4 – dichloropyridazin – 2 – yl, 3 – phenylcoumarin – 7 – yl, 4 – phenylcoumarin – 7 – yl, 6 – chloro – 4 – trifluoromethylcoumarin – 7 – yl, 4 – methylcoumarin – 7 – yl, 3 – (benzothiazol – 2 – yl)coumarin – 7 – yl, saccharin – 6 – yl, 4 – (4 – morpholinyl) – 1,2,5 – thiadiazol – 3 – yl, 5 – phenyl – 1,3,4 – thiadiazol – 2 – yl, 5 – phenyl – 1,3,4 – oxadiazol – 2 – yl, 3 – methylthio – 6 – methyl – 1,2,4 – triazin – 5 – yl, 4 – ethoxycarbonylisoxazol – 5 – yl, 1,2,5 – thiadiazol – 3 – yl, 2,5 – dioxopyrrolidin – 1 – yl, 2 – methyl – 4,5 – di(hydroxymethyl) – 3 – pyridyl, 5 – methoxycarbonylisoxazol – 3 – yl and 1 – methyl – 2 – ethoxycarbonylindol – 3 – yl.

Compounds of Formula I wherein L is O and $R^1$ is the residue of an oxime were prepared wherein the oxime residue is 2,5 – dioxopyrrolidin – 1 – yl and 3,4 – dihydro – 3 – oxo – 5 – phenylpyrazol – 4 – imino.

A compound of Formula I wherein L is O and $R^1$ is tricyclic substituted aryl was prepared wherein tricyclic substituted aryl is 1 – oxo – 7 – phenalenyl.

Compounds of Formula I wherein L is O and $R^1$ is monocyclic substituted aryl were prepared wherein monocyclic substituted aryl is 2,5 – difluoro – 4 – (4 – morpholinylsulfonyl)phenyl, 2,4 – dichloro – 3 – [2 – (4 – morpholinyl)ethoxycarbonyl)]phenyl, 2,4 – dichlorophenyl, 2,4,6 – trichlorophenyl, 2,4 – dichloro – 3 – (4 – methylpiperazinylcarbonyl)phenyl, 2,4 – dichloro – 3 – carboxyphenyl, 3 – [2 – (4 – morpbolinyl) – ethoxycarbonyl)]phenyl, 3 – (4 – methylpiperazinyl – carbonyl)phenyl, 2,4 – dichloro – 3 – [2 – (4 – morpholinyl)ethylaminocarbonyl]phenyl, 4 – (4 – morpholinylsulfonyl)phenyl, 2,4 – dichloro – 6 – (4 – morpholinyl – sulfonyl)phenyl, 2 – chloro – 4 – (4 – morpholinylsulfonyl)phenyl, 2 – methoxycarbonyl – 5 – methoxyphenyl,

2 – fluoro – 4 – (4 – morpholinylsulfonyl)phenyl, 2 – chloro – 4 – (4 – thiamorpholinylsulfonyl)phenyl, 2 – chloro – 4 – (4,4 – dioxy – 4 – thiamopholinylsulfonyl)phenyl, 2,6 – difluoro – 4 – (4 – morpholinylsulfonyl)phenyl, 2,4 – difluoro – 6 – (4 – morpholinylsulfonyl)phenyl, 3,4 – difluoro – 6 – (4 – morpholinylsulfonyl)phenyl, 2 – (4 – morpholinyl – sulfonyl) – 4 – fluorophenyl, 4 – [2 – (4 – morpholinyl)ethylaminocarbonyl]phenyl, pentafluorophenyl, 3 – (4 – methylpiperazinylsulfonyl)phenyl, 3 – (4 – morpholinyl – ethoxy)phenyl, 3 – [2 – (dimethylamino)ethyl)methylaminosulfonyl]phenyl, 4 – – methylsulfonylphenyl, 3 – diethoxyphosphonyl – phenyl, 2 – trifluoromethyl – 4 – (4 – morpholinylsulfonyl)phenyl, 2,6 – dichloro – 4 – (4,5 – dihydrooxazol – 2 – yl)phenyl, 3,5 – difluoro – 4 – (4 – morpholinylcarbonyl)phenyl, 3,5 – difluorophenyl, 2,5 – difluoro – 4 – (4 – methylpiperazinylsulfonyl)phenyl, 2,6 – difluoro – 4 – (4 – methylpiperazinylsulfonyl)phenyl, 3,5 – difluoro – 4 – (4 – morpholinylsulfonyl)phenyl, 2,6 – dichloro – 4 – ethoxycarbonylphenyl, 1 – oxocycloheptatrien – 2 – yl and 3,5,6 – trimethylquinon – 2 – yl.

A compound of Formula I wherein L is O and $R^1$ is monocyclic, substituted, hydroaromatic 3 – oxocarbocycl – 1 – enyl has been prepared wherein 3 – oxocarbocycl – 1 – enyl is 2 – methyl – 3 – oxo – 1 cyclopentenyl.

A compound of Formula I wherein L is O and $R^1$ is monocyclic, substituted, aromatic 3 – oxo – C – heterocycl – 1 – enyl has been prepared wherein 3 – oxo – C – heterocycl – 1 – enyl is 6 – methyl – 1 – pyron – 4 – yl.

Compounds of Formula I wherein L is S and $R^1$ is cyano, benzoyl and ethoxythiocarbonyl have been prepared.

Compounds of Formula I wherein L is S, SO or $SO_2$ and $R^1$ is monocyclic substituted aryl has been prepared wherein monocyclic substituted aryl is 2 – fluoro – 4 – (4 – morpholinylsulfonyl)phenyl.

Compounds of Formula I wherein L is S and $R^1$ is monocyclic, substituted, aromatic C – heterocyclyl have been prepared wherein monocyclic, substituted, aromatic C – heterocyclyl is 1 – phenyltetrazol – 5 – yl, 1 – [2 – (4 – morpholinyl)ethyl]tetrazol – 5 – yl, 1 – (dimethylaminocarbonylmethyl) – tetrazol – 5 – yl, 1 – (3 – pyridyl)tetrazol – 5 – yl, 1 – methyltetrazol – 5 – yl, 5 – methyl – 1,3,4 – thiadiazol – 2 – yl, 5 – cyclohexylamino – 1,3,4 – thiadiazol – 2 – yl, 1 – (4 – morpholinylpropyl) – tetrazol – 5 – yl, 5 – [2 – (4 – morpholinyl)ethylthio] – 1,3,4 – thiadiazol – 2 – yl, 5 – [2 – (1 – piperidinyl)ethylthio]1,3,4 – thiadiazol – 2 – yl, 5 – (2 – diethylaminoethyl) – 1,3,4 – thiadiazol – yl, 5 – (2 – dimethylaminoethylthio) – 1,3,4 – thiadiazol – yl, 5 – [2 – (4 – morpholinyl)ethyl] – 1,3,4 – thiadiazol – 2 – yl, 5 – [2 – (1 – piperidinyl)ethyl] – 1,3,4 – thiadiazol – 2 – yl, 5 – phenyl – 1,3,4 – oxadiazol – 2 – yl, 5 – (2 – furyl) – 1,3,4 – oxadiazol – 2 – yl, 1 – (3 – succinoylaminophenyl) – tetrazol – 5 – yl, 5 – benzyl – 1,3,4 – oxadiazol – 2 – yl, 5 – hydroxy – 6 – methyl – 6,7 – dihydro – 1H – 1,2,4 – triazolo[3,4 – b][1,3]thiazin – 3 – yl, 5 – (3 – pyridyl) – 1,3,4 – oxadiazol – 2 – yl, 1 – methyl – 5 – ethoxy – 1,3,4 – triazol – 2 – yl, 5 – (4 – trifluoromethylphenyl) – 1,3,4 – oxadiazol – 2 – yl, 5 – (4 – methoxyphenyl) – 1,3,4 – oxadiazol – 2 – yl, 5 – (4 – pyridyl) – 1,3,4 – oxadiazol – 2 – yl, 5 – (4 – biphenylyl)1,3,4 – oxadiazol – 2 – yl, 5 – (2 – pyrazinyl) – 1,3,4 – oxadiazol – 2 – yl, 4 – (ethoxycarbonylmethyl)thiazol – 2 – yl, 5 – (2 – pyridyl) – 1,3,4 – oxadiazol – 2 – yl, 5 – (3 – furyl) – 1,3,4 – oxadiazol – 2 – yl, 4 – ethoxycarbonyl – 5 – methylthiazol – 2 – yl, 4 – phenylthiazol – 2 – yl, 4,5 – dimethylthiazol – 2 – yl, 4 – (4 – morpbolinyl) – 1,2,5 – thiadiazol – 2 – yl, 3 – phenyl – 2 – thiono – 2,3 – dihydro – 1,3,4 – thiadiazol – 5 – yl, 4 – methyl – 5 – oxo – 6 – hydroxy – 4,5 – dihydro – 1,2,4 – triazin – 3 – yl, 5 – [4 – (n – pentyloxy)phenyl] – 1,3,4 – oxadiazol – 2 – yl, 5 – {4 – [2 – (2 – methoxyethoxy)ethoxy]phenyl} – 1,3,4 – oxadiazol – 2 – yl, 5 – (3,4 – methylenedioxyphenyl) – 1,3,4 – oxadiazol – 2 – yl, 5 – (2,5 – dimethoxyphenyl) – 1,3,4 – oxadiazol – 2 – yl, 5 – (2 – methoxyphenyl) – 1,3,4 – oxadiazol – 2 – yl and 5 – phenyloxazol – 2 – yl.

As stated above the compounds of Formula I inhibit the enzymatic activity of proteolytic enzymes and are useful in treatment of degenerative diseases. More particularly they inhibit human leukocyte elastase and chymotrypsin – like enzymes and are useful in treatment of emphysema, rheumatoid arthritis, pancreatitis, cystic fibrosis, chronic bronchitis, adult respiratory distress syndrome, inflammatory bowel disease, psoriasis, bullous pemphigoid and alpha – 1 – antitrypsin deficiency. This utility was demonstrated by an in vitro test of inhibition of compounds of Formula I against human leukocyte elastase.

Measurement of the inhibition constant ($K_i$) of a human leukocyte elastase inhibitor complex has been described (Cha, Biochemical Pharmacology, vol 24, pp. 2177 – 2185, 1975) for truly reversible inhibition constants usually concerning competitive inhibitors. The compounds of Formula I do not form truly reversible inhibitor complexes but rather are consumed by the enzyme to some extent. $K_i^*$, which is defined as the rate of reactivation of the enzyme divided by the rate of inactivation of the enzyme ($k_{off}/_{on}$), was therefore determined instead. The values of $k_{off}$ and $k_{on}$ were measured and $K_i^*$ was then calculated.

The value of $k_{on}$ was determined by measuring the enzyme activity of an aliquot of the enzyme as a function of the time after addition of the test compound (inhibitor). By plotting the log of the enzyme activity against time an observed rate of inactivation ($k_{obs}$) was obtained by the equation $k_{obs} = \ln 2/t_{1/2}$ wherein $t_{1/2}$ is the time required for the enzyme activity to decrease by 50%. The value of $k_{on}$ was then obtained by the

equation $k_{on} = k_{obs}[I]$ wherein [I] is the concentration of the inhibitor. The value of $k_{off}$ was similarly determined, and $K_i^*$ was then obtained by the equation $K_i^* = k_{off}/k_{on}$.

The results shown in Table I were obtained for the compounds of Formula I of Examples 1 – 3.

Table I

| Inhibition of Human Leukocyte Elastase | |
|---|---|
| Compound of Formula I of Example | $K_i^*$(nM) |
| 1 | 0.024 |
| 2 | 0.014 |
| 3 | 0.27 |

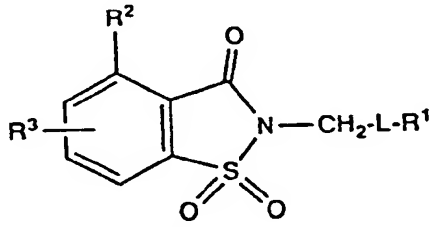
The other examples of the compounds of Formula I have $K_i^*$values in the range from about 1,000 nM to about 0.01 nM.

The proteolytic enzyme inhibiting amount of the compound of Formula 1 can be estimated from the results of the test for human leukocyte elastase inhibition and can additionally be varied for a particular patient depending on the physical condition of the patient, the route of administration, the duration of treatment and the response of the patient. An effective dose of the compound of Formula I can thus only be determined by the clinician after consideration of all pertinent criteria and exercise of best judgment on behalf of the patient.

A compound of Formula I can be prepared for pharmaceutical use by incorporating it in a pharmaceutical composition for oral, parenteral or aerosol inhalation administration, which can be in solid or liquid dosage form including tablets, capsules, solutions, suspensions and emulsions and which can include one or more suitable adjuvants. Solid unit dosages in the form of tablets or capsules for oral administration are preferred. For this purpose the adjuvant can be for example one or more of calcium carbonate, starch, lactose, talc, magnesium stearate and gum acacia. The compositions are prepared by conventional pharmaceutical techniques.

## Claims

**1.** A compound having the structural formula



Formula I

wherein

L is NO, O or $SO_n$ wherein n is 0, 1 or 2;

$L-R^1$ is a leaving group, $H-L-R^1$ is the conjugate acid thereof and,

when L is N, $H-L-R^1$ has a $pK_a$ value less than or equal to 6,

when L is O, $H-L-R^1$ has a $pK_a$ value less than or equal to 8, and

when L is $SO_n$, $H-L-R^1$ has a $pK_a$ value less than or equal to 5;

$R^2$ is primary or secondary alkyl of two to four carbon atoms, primary alkylamino of one to three carbon atoms, primary alkylmethylamino of two to four carbon atoms, diethylamino or primary alkoxy of one to three carbon atoms; and $R^3$ is from one to three substituents at any or all of the 5 –, 6 – and 7 – positions and is selected from the group consisting of hydrogen, lower – alkyl, cycloalkyl, amino – lower – alkyl, lower – alkylamino – lower – alkyl, di – lower – alkylamino – lower – alkyl, hydroxy – lower – alkyl, lower – alkoxy – lower – alkyl, perfluoro – lower – alkyl, perchloro – lower – alkyl, formyl, cyano, carboxy, aminocarbonyl, R – oxycarbonyl, B = N wherein B = N is amino, lower – alkylamino, di – lower –

alkylamino, carboxy – lower – alkylamino,1 – pyrrolidinyl, 1 – piperidinyl, 1 – azetidinyl, 4 – morpholinyl, 1 – piperazinyl, 4 – lower – alkyl – 1 – piperazinyl, 4 – benzyl – 1 – piperazinyl or 1 – imidazolyl, 1 – lower – alkyl – 2 – pyrrolyl, lower – alkylsulfonylamino, perfluoro – lower – alkylsulfonylamino, perchloro – lower – alkylsulfonylamino, nitro, hydroxy, lower – alkoxy, cycloalkoxy, B = N – lower – alkoxy, hydroxy – lower – alkoxy, polyhydroxy – lower – alkoxy or acetal or ketal thereof, lower – alkoxy – lower – alkoxy, poly – lower – alkoxy – lower – alkoxy, hydroxy – poly – lower – alkyleneoxy, lower – alkoxy – poly – lower – alkyleneoxy, B = N – carbonyloxy, carboxy – lower – alkoxy, R – oxycarbonyl – lower – alkoxy, methylenedioxy, di – lower – alkylphosphonyloxy, R – thio, R – sulfinyl, R – sulfonyl, perfluoro – lower – alkylsulfonyl, perchloro – lower – alkylsulfonyl, aminosulfonyl, lower – alkylamino – sulfonyl, di – lower – alkylaminosulfonyl and halo wherein R is lower – alkyl, phenyl, benzyl or naphthyl or phenyl or naphthyl having one or two substituents selected from the group consisting of lower – alkyl, lower – alkoxy and halo;

or a pharmaceutically acceptable acid addition salt thereof if the compound has a basic functional group or a pharmaceutically acceptable base addition salt thereof if the compound has an acidic functional group.

2. A compound as claimed in claim 1 wherein $R^2$ is primary or secondary alkyl of two to four carbon atoms and $R^3$ is hydroxy, lower – alkoxy, cycloalkoxy, B = N – lower – alkoxy, hydroxy – lower – alkoxy, polyhydroxy – lower – alkoxy or acetal or ketal thereof, lower – alkoxy – lower – alkoxy, poly – lower – alkoxy – lower – alkoxy, lower – alkoxy – poly – lower – alkyleneoxy, B = N – carbonyloxy, carboxy – lower – alkoxy, R – oxycarbonyl – lower – alkoxy, or methylenedioxy.

3. A compound as claimed in claim 2 wherein $R^2$ is isopropyl and $R^3$ is lower – alkoxy.

4. A compound as claimed in claim 3 wherein $R^3$ is 6 – methoxy.

5. A compound as claimed in claim 4 wherein L is N and H – L – $R^1$ has a $pK_a$ value less than or equal to 6.

6. A compound as claimed in claim 4 wherein L is O and H – L – $R^1$ has a $pK_a$ value less than or equal to 8.

7. A compound as claimed in claim 4 wherein L is $SO_n$ and H – L – $R^1$ has a $pK_a$ value less than or equal to 5.

8. A pharmaceutical composition comprising a proteolytic enzyme inhibiting concentration of a compound of Formula I as claimed in claim 1 and a pharmaceutical carrier.

9. A pharmaceutical composition comprising a proteolytic enzyme inhibiting concentration of a compound as claimed in any one of claims 2 to 7 and a pharmaceutical carrier.

10. The use of a compound of Formula I as claimed in claim 1 for preparation of a medicament for treatment of a degenerative disease in a patient in need of such treatment.

11. The use of a compound as claimed in any one of claims 2 to 7 for preparation of a medicament for treatment of a degenerative disease in a patient in need of such treatment.

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number

EP 92 20 3468

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| D,X | WO-A-9 013 549 (STERLING DRUG INC.)<br>* claims *<br>--- | 1-4,6-11 | C07D275/06<br>A61K31/425<br>C07D417/12 |
| A | JOURNAL OF HETEROCYCLIC CHEMISTRY.<br>vol. 26, no. 4, July 1989, PROVO US<br>pages 1073 - 1076<br>SAM-YOUNG CHOI ET AL 'Reaction of N-hydroxymethylsaccharin with aliphatic carboxylic derivatives:synthesis of N-acylsaccharins and N(saccharinylmethyl)aliphatic carboxylates'<br>* the whole document *<br>--- | 1-7 | |
| P,X | EP-A-0 483 928 (STERLING WINTHROP INC)<br>* claims *<br>----- | 1-4,6,<br>8-11 | |

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 03 FEBRUARY 1993 | HENRY J.C. |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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